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Office of Agricultural Biotechnology

Minutes

Agricultural Biotechnology Research Advisory Committee

June 21-22, 1990

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U.S. DEPARTMENT OF AGRICULTURE
AGRICULTURAL BIOTECHNOLOGY RESEARCH ADVISORY COMMITTEE
MINUTES OF MEETING

June 21-22, 1990

TIME, PLACE, AND PARTICIPANTS

The eighth meeting of the Agricultural Biotechnology Research Advisory Committee (ABRAC) took place on June 21-22, 1990, in Conference Room A of the American Institute of Aeronautics and Astronautics, 10th Floor, 901 D Street S.W., Washington, DC. The meeting was open to the public.

Members present included:

Bennie Osburn, Chair, University of California, Davis, CA;
Harold Hafs, Merck, Sharp and Dohme, Rahway, NJ;
William Witt, Food and Drug Administration, National Center for Toxicological Research, Jefferson, AR;
Frank Whitmore, Ohio State University, Wooster, OH;
John Kemp, New Mexico State University, Las Cruces, NM;
Sue Tolin, Virginia Polytechnic Institute and State University, Blacksburg VA;
Edward Korwek, Hogan and Hartson, Washington, DC;
George Hill, Meharry Medical College, Nashville, TN;
David Andow, University of Minnesota, St. Paul, MN;
Anne Vidaver, University of Nebraska, Lincoln, NE;
Lee Bulla, University of Wyoming, Laramie, WY;
David Kline, Iowa State University, Ames, IA;
Alvin Young, Executive Secretary and Director, USDA Office of Agricultural Biotechnology, Washington, DC.

The roster of Committee members is included as Appendix A.

USDA Office of Agricultural Biotechnology (OAB) staff present included: Daniel Jones, Maryln Cordle, John Gerber, Marshall Phillips, William Robinson, Paul Stern, Martha Steinbock, Marti Asner, Elsie Brown, Heidi Stockmoe, and Sheila Armen.

Others present for all or part of the meeting included:

D.R. Jagannath, FDA/Center for Veterinary Medicine
Allison Wilkins, USDA/Cooperative State Research Service
Leslie Coleman, American Veterinary Medical Association
Linda Lyons, American Veterinary Medical Association
Ellie Clark, EPA/Office of Toxic Substances
William Schneider, EPA/Office of Pestcide Programs
Robert Zimbelman, American Society of Animal Science
Eric Triplett, University of Wisconsin
Max McFadden, USDA/Forest Service
Loren Lange, USDA/Food Safety and Inspection Service
Connie Bacon, USDA/Food Safety and Inspection Service
Denise Clark, USDA/Food Safety and Inspection Service

John Gorham, USDA/Agricultural Research Service
Hiram Larew, U.S. Agency for International Development
Warren Springer, Northrup King Co.
Larry Zeph, EPA/Office of Toxic Substances
Jane Rissler, National Wildlife Federation
Patricia Michitsch, McDermott, Will, and Emery
Joan Murphy, Food Chemical News
Pedro Barbosa, University of Maryland/Ecological Society of America
John Payne, USDA/Animal and Plant Health Inspection Service
Eric Flamm, Food and Drug Administration
Anne Guthrie, Capitol Associates
Frank Bass, Bureau of National Affairs
Lisa Zannoni, USDA/Science and Education
Michael Broder, EPA/Office of Toxic Substances
Ivan Spilda, Slovak Technical University, Bratislava
Eric Ottewitte, Idaho National Engineering Laboratory
Carol Ezzell, BioWorld

CALL TO ORDER, INTRODUCTION OF NEW MEMBERS, AND APPROVAL OF AGENDA AND MINUTES

Dr. Bennie Osburn, Chair, called the meeting to order at 9:06 a.m. The Committee approved the agenda as distributed.

Dr. Osburn introduced Dr. William Witt, a new member, and Dr. George Hill, a former alternate now a member of the Committee. Dr. Osburn noted that three members, Drs. Ann Sorensen, Deborah Letourneau, and Hugh Bollinger, were not in attendance.

Dr. Rissler, National Wildlife Federation, asked who replaced former ABRAC member Anne Hollander. Dr. David Kline replied that he had replaced Ms. Hollander. Dr. Young indicated that the slot Ms. Hollander formerly occupied on the Committee is an interdisciplinary one concerned with bioethics, environmental policy, and public attitudes.

Dr. Osburn turned the Committee's attention to the minutes of the previous meeting. Dr. Andow submitted written changes in the minutes. Dr. Korwek said that the discussion of the exemption in Section III-B-5 on p. 19 of the minutes did not comport with his recollection of what transpired at the previous meeting. Dr. Tolin said that a number of passages in the minutes needed revision. Dr. Osburn asked the OAB staff to review the transcript of the previous meeting and he invited ABRAC members to submit written changes. Dr. Young indicated that OAB would provide ABRAC members with the original minutes, the meeting transcript, and a proposed rewrite for the parts of the minutes in question. The Committee unanimously tabled approval of the minutes.

NEPA PROCESS FOR RESEARCH GUIDELINES

Dr. Young referred to the Committee's vote at the previous meeting on submitting a working draft of the guidelines for development of an environmental impact statement (EIS) under the National Environmental Policy Act (NEPA). He said the current draft (Document # 132) reflects the Departmental draft at the current time, and not the previous ABRAC vote exclusively. Dr. Young indicated there are other proceedings that may affect the guidelines such as the ongoing "scope of organisms" effort of the Biotechnology Science Coordinating Committee (BSCC). He pointed out that the proposed action in an EIS process must be amenable to change based on information collected in the public comment period and public meetings and he invited ABRAC members to submit comments on the proposed action when it is published if they are so inclined.

Dr. Korwek expressed concern about the procedure being followed. He questioned the relationship between Document # 132 and what the Committee had voted on at its previous meeting.

Dr. Young replied that the Committee was intended to provide advice to the Department which bears primary responsibility for entering the guidelines into the EIS process. He indicated that the changes in the scope section and appendices reflect the Federal government's position at the present time.

Dr. Korwek asked what specific recommendations of the ABRAC were not accepted by the Assistant Secretary.

Mr. Stern replied that the Assistant Secretary accepted the ABRAC document with the exception of selected text in the scope sections III-B-4a and III-B-5.

Dr. Korwek noted that, in his view, there is a conflict between Section III-B-5 and the minutes of the previous meeting.

Dr. Tolin acknowledged that there may have been a lack of clarity at the previous meeting. She recollected that the Committee had approved the language "other specific organisms approved by USDA," but that she preferred the language in Document 132.

Dr. Korwek disagreed, saying that he had a problem with the language in Section III-B-5 about "familiarity."

Dr. Kemp asked if the second sentence in Section III-B-5 of Document 132 had been approved by the ABRAC.

Dr. Young replied that it had not. He said the language in question was inserted at the direction of the Assistant Secretary and that it may be necessary to change it again depending on the final definition of scope developed by the

BSCC. Dr. Young said that OAB would share the scope definitions of ABRAC, BSCC, and USDA with the Committee members.

NOTICE OF INTENT TO PREPARE GUIDELINES

Dr. Osburn asked Mr. Robinson to update the Committee on the notice of intent (NOI) to prepare guidelines. Mr. Robinson indicated that an NOI is required for an EIS effort by NEPA and by Council on Environmental Quality (CEQ) regulations. He outlined the structure and content of an NOI including descriptions of the proposed action, appropriate alternatives, and the scoping process.

Dr. Rissler asked if ad hoc reviews by ABRAC would continue during the EIS process. Dr. Young replied that he expected case-by-case reviews by the ABRAC to continue during the EIS process. He said he hoped to have the EIS finalized and the research guidelines in place by 1992 after which there may be sufficient knowledge and experience to move away from strict case-by-case review.

Dr. Rissler asked if the BSCC scope definition would be up for change during the EIS process. Ms. Cordle replied that the BSCC scope definition will be published in the Federal Register for public comment in a separate proceeding. Dr. Korwek offered the interpretation that development of the BSCC scope definition is a policy initiative not subject to NEPA.

LAY SUMMARY

Dr. Osburn turned the Committee's attention to the lay summary of the guidelines. Mr. Robinson described it briefly and Dr. Young noted that the lay summary has been distributed to the BSCC, cooperating agencies, the USDA Office of the General Counsel, and the Vice President's Council on Competitiveness.

COOPERATING AGENCIES

Dr. Tolin asked which agencies were cooperating agencies. Ms. Cordle replied that the agencies that were invited to become cooperating agencies for the EIS process were the Cooperative State Research Service, Agricultural Research Service, Forest Service, Food Safety and Inspection Service, Agricultural Marketing Service, Economic Research Service, Animal and Plant Health Inspection Service, Food and Drug Administration, National Institutes of Health, Department of Interior, Fish and Wildlife Service, Department of Commerce, Environmental Protection Agency, Department of Defense, Department of Energy, and the National Science Foundation.

Dr. Young indicated that the goal of his office is to have the Federal government adopt the USDA guidelines for field testing. He noted that everyone would benefit from a single set of research guidelines based on scientific considerations that

could evolve with increasing scientific knowledge and field testing experience.

Dr. Hill asked if the ABRAC will be involved in the comment process on the guidelines. Dr. Young replied that he plans to support the attendance of two ABRAC members at each scoping session and that specific issues identified in the scoping sessions may be placed on the ABRAC agenda.

APPENDICES

Dr. Osburn turned the attention of the Committee to the appendices of the guidelines. Dr. Phillips outlined the content of Appendix 1 which contained 5 examples of the determination of the level of safety concern for several genetically modified organisms. He also invited the Committee members to suggest changes in the table of examples. Dr. Young noted that principal investigators and Institutional Biosafety Committees will need specific examples in order to understand fully the assignment of levels of safety concern.

Dr. Andow suggested the addition of two more columns to the table of examples for environment and the trait modified. Dr. Gerber replied that the text accompanying the tables specified geographic locations and thereby specific environments for the examples. [OAB staff note: Table 1/Appendix 1 in Document 132 applies to parental organisms, so the trait to be modified would not necessarily be known.]

Dr. Kemp expressed concern that the geographic difference in the examples he submitted had not been retained in this version of the guidelines.

Dr. Gerber replied that Dr. Kemp's examples were detailed and commendable in their geographic/climatic contrast, but that none of the other examples included that feature. Dr. Gerber said the geographic/climatic difference for that particular example was omitted from the guidelines only for editorial consistency. [OAB staff note: Dr. Kemp's examples, including geographic/climatic differences, are included in the minutes of the ABRAC Working Group on Classification of Unmodified Organisms, June 22-23, 1989, Document No. 89-WG-02].

Dr. Andow expressed concern about alternatives to the guidelines, the relationship of ABRAC to the NEPA process, and the need for ABRAC subcommittees or working groups on the EIS.

Dr. Young replied that he planned to send two ABRAC members to each scoping session to answer scientific questions that might arise. He said he would welcome questions and comments on the EIS process from ABRAC members, but he had not planned to convene a special ABRAC working group on the EIS.

Dr. Andow asked for a sense of the Committee on the structural aspects of the EIS effort. Dr. Bulla expressed the view that it might be more constructive to digest the guidelines and comment on them as appropriate during EIS development rather than to convene a working group now that lacked a focus on specific issues. The sense of the Committee was for a more formal structure for ABRAC input to the EIS effort and Dr. Andow was asked to provide a proposal for such a scheme.

Dr. Whitmore and Dr. Tolin noted that in past meetings, the ABRAC had considered and rejected many alternatives related to the research guidelines. Mr. Robinson observed that the ABRAC could be very helpful to the interdisciplinary EIS team in determining which alternatives to consider in more detail.

REGIONAL SCOPING SESSIONS

Dr. Osburn turned the Committee's attention to the upcoming regional scoping sessions. As background for that discussion, he outlined the ABRAC's past deliberations on biosafety review including 3 steps of risk assessment, reviews of the unmodified organism, the genetic change, and the modified organism, and 2 steps of risk management, determination of appropriate confinement measures and the appropriate organizational level of safety review.

Dr. Gerber summarized the current OAB plans for scheduling, conducting, and analyzing the regional scoping sessions for development of the EIS. Mr. Robinson and Dr. Phillips engaged in a brief role-playing exercise to illustrate the kinds of confrontational situations that can arise in public scoping sessions.

Dr. Kline noted the fine distinction between explaining and defending a proposal at public gatherings such as the scoping sessions. Mr. Robinson pointed out that it is the responsibility of the chair of a public scoping session to control attempts at filibustering and other departures from orderly conduct of the session. Dr. Andow, noting the absence of a scoping session in the corn belt, recommended the scheduling of a scoping session somewhere in the corn belt area of the country.

Dr. Tolin opened the comments of the primary reviewers on framing the scientific issues at the scoping sessions. She supported the division of the steps under the guidelines into risk assessment and risk management. She supported a focus on scientific issues at the scoping sessions rather than on the scope of organisms covered under guidelines and regulations. She emphasized consideration of the unmodified organism as the baseline for biosafety evaluations and she expressed the view that research with organisms that are generally recognized as compatible with the environment (GRACE) does not require any special confinement measures. She concluded by referencing the

Classification Working Group meeting of June, 1989, and noted that its approach was based in large part on the recommendations of the Ecological Society of America.

Dr. Vidaver noted that there is already a great deal of knowledge about the behavior of many organisms in agricultural research. She envisioned the current situation as how to accommodate concerns for the risk of research with modified organisms with what is known about the previous behavior of organisms in agricultural research. She emphasized that the research community must try to accommodate public concerns about the safety of research and still allow agricultural research to proceed in an orderly manner.

Dr. Kemp recalled that the guideline effort was earlier confronted with the question of whether biotechnology oversight should be process-driven or product-driven, and that a consensus seems to have developed that it should be product-driven. Dr. Tolin reminded the Committee that the process by which a genetic change is accomplished may often have to be considered in assessing the risk of that genetic change in an organism.

In preparation for the upcoming scoping sessions, Dr. David MacKenzie, at the Chair's request, conducted a nominative group exercise on the question of what scientific issues contribute to the guidelines and what issues detract from the guidelines. In the course of this exercise, over 90 issues were identified and they are summarized in Appendix B.

Dr. Osburn asked Dr. Kline to address some of the issues other than scientific ones that might arise in the scoping sessions. Dr. Kline noted that the guidelines do not address the normative or acceptable component of risk. Instead, in his view, the guidelines focus on conditions or confinement measures to reduce the possible risk to a negligible level. He indicated that he was generally comfortable with this approach, but it might need to be explained carefully to the public during the scoping sessions.

Dr. Korwek noted that government agencies determine acceptable risk all the time when there are countervailing benefits to certain technologies. Dr. Payne added that a significant amount of academic research involves risk that is greater than negligible, but it has been determined to be generally acceptable by society. Dr. Andow pointed out that ecologists and laboratory scientists often disagree on the amount of data that is sufficient to provide a basis for acceptable risk decisions.

Dr. Korwek compared the risk vocabulary of the the NIH Guidelines with that of the draft USDA guidelines. He pointed out that the NIH Guidelines use the phrase "absence of significant risk." In his view, negligible risk is a very

stringent standard and it is different from the absence of significant risk.

ALTERNATIVES

Dr. Osburn asked Mr. Robinson to brief the Committee on the identification of alternatives in the EIS process. Mr. Robinson stated that NEPA is a procedural act that requires Federal agencies to explore and evaluate alternatives to the proposed action. He said it is usually helpful if the formulation of alternatives begins early in the EIS process.

Dr. Whitmore asked if the proposed action in this case is to allow research to move forward or to adopt the guidelines. Mr. Medley expressed the view that the proposed action is not adoption of the guidelines themselves but what the guidelines do.

Dr. Kemp asked if USDA can support biotechnology research without an EIS. Mr. Robinson said the agency does not have to prepare an EIS, but it does need to comply with NEPA. He said that development of an EIS can simplify subsequent case-by-case actions, but it may still be necessary in some instances to prepare environmental assessments. Mr. Robinson related to the Committee his previous experience that the development of one EIS often saved money for the U.S. Forest Service compared to the development of many environmental assessments and related legal challenges.

Dr. Osburn recessed the meeting until the following day.

June 22, 1990

FSIS PROPOSED CRITERIA FOR SLAUGHTER OF NON-TRANSGENIC ANIMALS FROM TRANSGENIC ANIMAL EXPERIMENTS

Dr. Osburn reconvened the meeting. He referred the Committee to Document 133 which describes the Food Safety and Inspection Service (FSIS) proposed criteria for dealing with "non-transgenic" animals from transgenic animal experiments. He then introduced Dr. Connie Bacon, FSIS.

Dr. Bacon thanked the Committee for the opportunity to present the proposed criteria FSIS is considering for the inspection of "non-transgenic" animals from transgenic animal experiments. She said FSIS is responsible under Federal statutes for ensuring that meat and poultry and products derived from livestock and poultry are wholesome, not adulterated and labeled properly.

Dr. Bacon noted that there have been tremendous advances in research on transgenic animals since 1982 when the first transgenic animal, a mouse, was produced. She said that in the future biotechnology may lead to faster growing livestock with

natural resistance to many diseases. She said that FSIS is striving to keep up with the new technology.

Dr. Bacon pointed out that transgenic livestock have proved to be difficult to produce. In the case of cattle, the success rate is less than 2 percent. This means that a large proportion of "non-take" animals are produced. Thus, this type of research is very expensive and researchers wish to be able to slaughter the non-transgenic animals in order to recoup some of the research costs.

Dr. Bacon stated that there are two methods which can be used to detect the transgene in animals from embryos which have been microinjected with DNA. These methods are Southern hybridization and the polymerase chain reaction (PCR). The PCR method, according to Dr. Bacon, is the more sensitive.

She said that FSIS proposes to use these two methods to detect the transgene. Animals would also be tested to see if there is a measurable transgene product, and evaluated to determine if they have a healthy phenotypic appearance. If an animal meets these criteria it would not differ from livestock which are produced traditionally. Thus the animal could be presented for slaughter according to 9 CFR 309.17, "Livestock Used in Research." This regulation stipulates that the researcher must provide to the agency certain information such as data on the research methods used and any pharmaceutical products administered to the animal. She said research animals must also be separated at the time of slaughter and inspected together, so that experiment-related pathology can be detected.

Dr. Bacon concluded her presentation by noting that if the animal is found to be transgenic it would be evaluated under separate criteria which are currently being drafted by FSIS.

Dr. Osburn commented that there has been a request to slaughter "non-transgenic" animals resulting from transgenic animal experiments. He commended FSIS for their approach and for giving the ABRAC an opportunity to review and comment on the proposal. He asked Dr. Bacon where and when will the Southern hybridization and PCR be performed?

Dr. Bacon responded that the tests would be done during the research process by the researcher. If the researcher fails to present enough data to FSIS, they can be asked to repeat the tests.

Dr. Osburn asked who will keep the gene bank? He also asked if FSIS will be in a position to conduct the tests themselves?

Dr. Bacon replied that FSIS personnel would not conduct the tests themselves. There are no processes in place for this at this time.

Dr. Witt noted that it is in the best interest of the researcher to identify animals as soon as possible. He said that, although the proposed process made FSIS dependent on the researcher, this is a good approach. Given the low efficiency of production of transgenic animals, researchers will administer the tests responsibly. He asked if these tests are sufficiently sensitive?

Dr. Hafs replied that most researchers believe the tests to be sufficiently accurate and specific. He asked Dr. Bacon how many animals would fall under these new procedures?

Dr. Bacon said it was difficult to estimate the number of animals involved, but the number would probably be in the hundreds.

Dr. Hafs commented on the FSIS proposal. He noted that research on cattle was farther along than research on other species, so that most of the requests would involve slaughter of cattle. He said that if an animal were truly transgenic, then these procedures would detect the transgene without any problems. However, if an animal were a mosaic, the transgene might not show up in muscle or fat tissue. For example, if the bovine somatotropin gene were modified, the transgene might only be present in the pituitary gland. He asked if FSIS had considered this problem?

Dr. Bacon replied that most transgenic livestock are produced by microinjection of one cell embryos and mosaics have not been reported from this method. The exact procedure used by the researcher must be described in the application for slaughter. Therefore, it would be known if the planned outcome is a mosaic with the gene in only one tissue.

Dr. Hafs agreed. He asked Dr. Bacon if the FSIS proposal covered work with viral vectors?

She replied that there is not much livestock work with viral vectors being done. If this work does proceed, the vector will first be evaluated by APHIS and then the food safety issue will be addressed by FSIS.

Dr. Osburn noted that it is possible to modify livestock using viral vectors, as well as by injecting transfected cells into bone marrow.

Dr. Hafs said that he wished to compliment FSIS on their far-sighted proposal. He said the process suggested was ample to protect the public.

Dr. Hill said he was concerned that the approach relied on the researcher to submit data. He asked if there was any way that FSIS could do the tests independently?

Dr. Bacon replied that U.S. regulatory agencies, including FDA and APHIS, traditionally rely on researchers to submit data. In our regulatory system the burden of proof is on the researcher. Dr. Osburn concurred that this is the approach used in the United States.

Dr. Korwek said that it was a good proposal. He asked what are the exact criteria proposed? He said the criteria should be listed more explicitly. This would also be useful for the researcher. He said he was also concerned about the mosaic issue. He said it might be possible for a researcher to unintentionally create a mosaic, and the proposed tests would miss it.

Dr. Bacon replied that for mice this could be a problem, but for livestock produced through microinjection the transgene would be detectable in any of the animals cells.

Dr. Korwek asked what happens to DNA which is injected, but not incorporated?

Dr. Bacon said that it is degraded in the cell. She said that in livestock, microinjection must take place at the one cell stage, otherwise the DNA is not incorporated with great enough efficiency.

Dr. Korwek referred to the regulation under which FSIS is considering this procedure. He said he believed the regulation pertained to other types of products used in the livestock industry. He questioned whether FSIS was stretching the regulation too far?

Dr. David Berkowitz, FSIS, replied that the regulation in question applies broadly to research. He said for the time being the regulation is legally sufficient to cover the situation; however when breeding of transgenic livestock for commercial purposes begins, the situation may be less clear.

Dr. Korwek said he did not believe the situation is so clear, particularly with regard to research versus commercial application of this technology.

Dr. Osburn said that researchers have been working under this statute for some time and that it covers control animals as well as animals which are the subjects of research. Dr. Hafs agreed that researchers know when they are doing research, but he added that the language may need to be amended.

Dr. John Payne from APHIS noted that retroviruses are not covered. Dr. Osburn said that there is interest in working with retroviruses.

Dr. Kline asked if there had been any unforseen genetic changes reported which resulted from the microinjection technique?

Dr. Bacon replied that none had been reported.

Dr. Kemp said that from the point of view of molecular biology, he was satisfied with the proposal. He said it is in the best interest of the researcher to identify transgenic animals. He said researchers would keep looking until they were certain the animal was not transgenic, and thus the risk of non detection was very low.

Dr. Andow asked if researchers would be required to use proper controls when performing the Southern hybridization and the PCR analyses, so they would be sure the weren't getting false readings.

Dr. Bacon said that negative control animals which had never been manipulated were required to be tested using the same procedures as test animals, as well as positive controls.

Dr. Andow said he was concerned about the issue of mosaics. He said there is evidence in humans that there is movement within the genome. He added that he would like to have a numerical estimate of the number of cells with the transgene which would be necessary for the test to be accurate.

Dr. Bacon replied that the tests proposed would work if the transgene were in 10% of the cells or perhaps even fewer for livestock. She said tissue samples are usually tested from each animal's ear or tail as well as blood. This and the additional criteria of testing for gene products and screening the phenotypic appearance of the animal would also help ensure adequacy.

Dr. Berkowitz said he would like to address Dr. Korwek's earlier question about the exact criteria. He said FSIS wanted to rest on the state-of-the-art without going into a discussion of a constantly decreasing level of detection. He said for the purposes of this proposal, such a discussion would not be useful. He restated the points made in the FSIS document which makes it clear that if no transgene were detected using the two tests, and there is no gene product, and no phenotypic change, then the animal could be considered the same as a traditional animal.

Dr. Andow disagreed, stating that the details of the proposal should be clarified, including the technical limitations of the tests. Dr. Vidaver added that illustrative examples might be useful.

Dr. Tolin complimented FSIS on the concepts used in the proposal. She agreed with FSIS that the PCR is sufficiently accurate to identify transgenes in livestock. She suggested that FSIS clarify to which species the proposal applies.

Dr. Bacon stated that the proposal applies to livestock, i.e., cattle, pigs, sheep and goats.

Dr. Tolin asked if the protocols looked at all the DNA which is injected?

Dr. Bacon said that the DNA injected into an embryo normally contains three functional domains, the promoter, the structural gene, and the enhancer. She said the probe used in the analysis should span all three sequences.

Dr. Tolin asked if the FSIS proposal covered the progeny of transgenic livestock?

Dr. Bacon said that at this time the proposal does not cover progeny. She said this issue would be covered in the FSIS proposal for transgenic animals which is being developed.

Dr. Whitmore said that he would like to compliment FSIS on its far-sighted approach and other members agreed. He said that USDA has just begun to discuss mapping the animal genome. He said FSIS is attempting to keep up with technology.

Dr. Osburn called for the sense of the committee. Dr. Kemp moved that the committee recommend that the process followed by FSIS be approved. The motion was seconded.

Dr. Korwek reiterated that FSIS should lay out the criteria in the procedure more explicitly.

The motion was passed by voice vote, 11 in favor, none opposed, and one abstention.

Dr. Jane Rissler, the National Wildlife Foundation, commented that she had heard several concerns raised by Committee members during the discussion. She asked why the ABRAC had approved the proposal without clarifying these issues. She said she was concerned that ABRAC was becoming a rubber stamp for the biotechnology industry. She said that ABRAC should ask FSIS for another iteration of the proposal which would clarify such issues as explicit criteria and the detection limits of the tests.

Dr. Osburn stated that ABRAC had approved the process that FSIS was adopting, not the specifics of the proposal. Other members expressed similar opinions.

Dr. Kemp asked if it would be possible to formally ask FSIS to keep ABRAC informed as they developed their approach, and to respond to some of the points that ABRAC had raised?

Dr. Osburn said that this would be appropriate. He asked OAB to draft a letter to FSIS to this effect.

Dr. Andow asked that the motion be voted on again to clarify that it indicated support for the process that FSIS was using.

Dr. Kemp moved that ABRAC approve the process being used by FSIS to deal with nontransgenic animals resulting from research on transgenic livestock. The motion was seconded. It passed unanimously.

UPDATE ON UNIVERSITY OF WISCONSIN EXPERIMENT ON GENETICALLY ENGINEERED RHIZOBIA

Dr. Osburn stated that Dr. Eric W. Triplett, Associate Professor, University of Wisconsin, Madison, had been requested to provide ABRAC with an update on his research which involved plans to field test genetically modified rhizobia.

Dr. Young noted that the experiment proposed by Dr. Triplett had been submitted to APHIS for a courtesy permit, and to the Cooperative State Research Service (CSRS) which had decided to prepare an environmental assessment (EA) on it. He said the intent of the Department was to move the experiment along, and to issue a single document on it. Thus, APHIS and CSRS would work together on the EA. Dr. Young clarified that the item had been placed on the ABRAC agenda for information only, and that ABRAC did not need to vote on the experiment, because action had already been taken by the Department on the experiment.

Dr. Triplett passed out an information packet on his proposed experiment which is attached as Appendix C. He described the experiment as an attempt to develop competitive, superior strains of rhizobium and bradyrhizobium. He said the aim of his work was to address the failure of superior inoculum strains to improve legume productivity in soils with a large indigenous population of rhizobia.

Dr. Triplett stated that his approach involved identifying a highly competitive strain, determining the basis of its competitiveness, isolating the genes involved in competitiveness, and transferring those genes to superior rhizobia. The strain he and his colleagues identified as highly competitive is R. leguminosarum bv. trifolii T24, which was first isolated from clover nodules in 1937. He said he had named a peptide from this strain trifolitoxin, although this is a misnomer because it is not a toxin.

The next step was to study the spectrum of trifolitoxin activity. Several strains of R. leguminosarum are trifolitoxin sensitive including R. leguminosarum bv. trifolii, viceae and phaseoli. On the other hand, R. meliloti and Bradyrhizobium japonicum are trifolitoxin resistant. Other bacterial genera resistant to trifolitoxin include Agrobacterium, Pseudomonas, Erwinia, Clavibacter, etc. Many fungi, plants and animals including chicken and man are unaffected by trifolitoxin.

Dr. Triplett then described the bacteriocin production by T 24 responsible for nodulation competitiveness and the transfer of trifolitoxin to effective rhizobia. He also presented a summary of trifolitoxin genetics in T24.

Dr. Triplett said the proposed field test was to see if trifolitoxin in rhizobium provide a competitive advantage for nodulation under agricultural conditions. He said the test would compare isogeneic strains of rhizobium which differ only in trifolitoxin production with the wild-type strain. The field experiment would determine if bacteriocin production by a rhizobium strain in the field affects a number of factors including: nodule occupancy; rhizosphere colonization; the population sizes of bacteriocin-sensitive and resistant species of indigenous rhizobia; total soil biomass; survival of the inoculum strain; and spread of the inoculum strain.

Dr. Triplett described the two sites, Arlington and Hancock, Wisconsin, proposed for the field experiment. He presented data on the two sites including soil type, drainage, rainfall, elevation, terrain, and previous crop. He said that indigenous clover and pea rhizobia at both sites are trifolitoxin sensitive.

He then described the recipient strain, TA1, noting that it does not move in soil, it has an average survival rate in soil, the genetics of nodulation is well characterized, specific antibodies are available, and it is highly effective on white and red clover.

Dr. Triplett reviewed the experimental design for the field test. He said it would involve seed inoculation of red clover using three inoculum strains and five inoculum levels. There would be five replicates at the two sites using a randomized complete block design. The sites would be monitored for nodule occupancy, movement, survival, rhizosphere colonization, effects on rhizobia in soil and total soil biomass. Dr Triplett said that if the recombinant strains spread in the soil that a number of actions would be taken including lowering the pH with elemental sulfur, fumigation, broad spectrum antibiotics, chlorate application , and bacteriocin production by R. melioti 102F69.

Dr. Triplett said the funding for the entire research project totalled $138,844. Sources of the funding included a USDA competitive grant, the Wisconsin applied research program, the University of Wisconsin graduate school, and Hatch Act funds.

Dr. David MacKenzie, CSRS, commented on the experiment. He said that APHIS and CSRS were working together to develop an EA for the proposed field test. He said a draft EA had been prepared and circulated to six reviewers. The EA included consideration of two alternatives including no action and the joint review by APHIS and CSRS with APHIS issuing a courtesy permit. He said

the EA covered such areas as the molecular biology of rhizobia, ecology, experimental design, biological monitoring procedures, remediation and evaluation. Dr. MacKenzie concluded by saying that if the USDA Guidelines had been in place, Dr. Triplett's proposal would have been handled by the IBC.
Dr. Payne said that there had been no technical triggering of NEPA; however, the EA was being prepared for administrative purposes.

Dr. Bulla said the name trifolitoxin raised concerns in peoples' minds. He asked if Dr. Triplett had considered changing the name. Dr. Triplett replied that he had not.

Dr. Kemp asked how many genes are involved? Dr. Triplett said that he didn't know yet. He added that they are currently trying to sequence it, and should know by this summer.

Dr. Kemp stated that he is personally very comfortable with the biosafety of the experiment because he is familiar with how difficult it is for rhizobia to persist in Wisconsin soils. He asked if Dr. Triplett had done some preliminary studies with indigenous strains. Dr. Triplett replied that he had not yet performed such studies.

Dr. Vidaver asked how many strains were examined? Dr. Triplett replied they had looked at about 200.

Dr. Andow asked if ABRAC would receive the final EA. Dr. Payne said they would.

Dr. Vidaver asked how long it had taken to get the experiment underway relative to other field work with nonmodified organisms. Dr. Triplett said that if no review had been required the experiment would have been begun in April 1989 and would have been fully underway by now. Dr. Hill asked how long the experiment would last once underway. Dr. Triplett said it would involve three years of field work.

Dr. Korwek asked why ABRAC had been asked to discuss the experiment? Dr. Young replied that the request for review had come into APHIS and CSRS because the Guidelines are not in place. He said he wanted the ABRAC to be kept informed of what is going on.

Dr. Korwek asked if the current discussion would be construed as <u>de facto</u> support for the experiment by ABRAC? He said that ABRAC had not been given enough data to approve the project; however, if the committee did nothing it might be misinterpreted as support.

Dr. Payne said there is no intention of considering the current discussion as an ABRAC review. Dr. Osburn said that the presentation is an informational item, so that the committee could see the NEPA process.

Dr. Kemp pointed out that the ABRAC had heard two proposals that day, one on which they had taken a vote, and the current one which is for information only. He said that the Committee needed to have a formalized process for hearing proposals.

Dr. Rissler commented that there is disarray in the Federal Coordinated Framework and that the handling of this proposal reflects this. She said that Dr. Triplett had contacted EPA, but had not received a review from EPA. He had received opinion letters form APHIS and NIH. The National Wildlife Federation has asked OAB to submit the proposal to ABRAC for review. But she now understands that another option is being pursued, which makes the handling of the proposal confusing.

Dr. Young stated that CSRS, not OAB, had reviewed the proposal. Dr. Korwek said that perhaps the proposal should have been submitted to ABRAC, but it had been submitted and acted upon elsewhere first.

Dr. Payne said that an opinion letter is more than just a letter, it also involves review of data. He said the opinion letter indicated the experiment did not involve a plant pest, interpreting the definition of plant pest very broadly. Thus, the experiment did get a risk-based review. On the basis of this review, NIH also said it would not act on the proposal. Dr. Triplett then came back to APHIS to ask for a courtesy permit. [OAB staff note: APHIS issues courtesy permits for organisms which are not regulated but which may be similar to organisms which are regulated (7 CFR 330.208)].

Dr. Korwek said that there is a funding standard which is not being addressed.

Dr. Rissler stated that if it is decided that APHIS did review the proposal, then that would be adequate. She said she was illuminating this issue, not because the experiment is risky, but because until oversight is in place cases like this must get careful review. She said this case had not afforded opportunity for public interaction.

Dr. Triplett agrees that researchers need a clear regulatory path. He said he had discussed his proposal with seven different agencies.

Dr. Tolin asked if NIH had issued an opinion letter. Dr. Payne said that they had. He said opinion letters are available to the public upon request. Dr. Rissler said that the public needed to be informed in order to be able to request these letters.

Dr. Tolin noted that Dr. Triplett had used the National Research Council Report, the USDA draft guidelines and the Ecological Society of America guidelines in preparing the documentation for

his project. She asked how useful these documents were and how well did they work? Dr. Triplett replied that he preferred the NRC document because, in his view, it focused more on product than on process.

REPORT ON A GROUP TECHNIQUE ANALYSIS OF THE USDA GUIDELINES

Dr. Osburn asked Dr. MacKenzie to report on the analysis of the USDA Guidelines which had been developed the day before using a special group technique.

Dr. MacKenzie distributed a draft summary of the features and issues related to the Guidelines which had been identified during the meeting the previous day. A draft is included as Appendix B.

Dr. Tolin said that some of the statements made by the committee members had been misinterpreted. For example, she had commented that the Guidelines address the accessible environment, and had considered this to be a positive attribute. However, Dr. MacKenzie had recorded her comment as a potential problem.

Dr. MacKenzie asked the Committee members to review the list of issues and inform him of any other misinterpretations or errors.

INTERNATIONAL SYMPOSIUM ON THE BIOSAFETY RESULTS OF FIELD TESTING GENETICALLY MODIFIED PLANTS AND MICROORGANISMS

Dr. Young announced that OAB, APHIS, Clemson University and several private companies are co-sponsoring an International Symposium on the Biosafety Results of Field Tests of Genetically Modified Plants and Microorganisms, November 28-30, 1990 on Kiawah Island, South Carolina.

The Symposium will assemble individuals from private firms, government, and academia throughout the United States, Europe, Asia, and the Pacific who have had first-hand experience with field testing genetically modified plants and microorganisms. The objective will be to discuss the biosafety issues and lessons learned as a result of these tests. The symposium will not cover the commercial results of the products being tested.

Dr. Young said that he hoped that ABRAC members would be able to attend the Symposium, and that he would look into the possibility of holding the next ABRAC meeting near Charleston, South Carolina so that this would be possible.

UPDATE ON AUBURN PROPOSAL ON TRANSGENIC CARP

Ms. Maryln Cordle reported on the Environmental Assessment (EA) which OAB had prepared on the Auburn proposal. She noted that questions had been raised about the impact on the environment if the fish escaped. As a result, OAB had been working with a number of fish experts in redrafting the EA. She said OAB would

be reaching a decision shortly on whether the revised EA could support a Finding of No Significant Impact (FONSI).

UPDATE ON TEXAS A&M BRUCELLOSIS PROPOSAL

Dr. Osburn asked Dr. Payne to report on the APHIS decision on the Texas A&M proposal. Dr. Payne said he was not prepared to report on this issue. Dr. Marshall Phillips, OAB, said that he understood from discussions with APHIS staff members that the experiment had been approved and that Texas A&M is ready to proceed.

UPDATE ON BSCC SCOPE DISCUSSIONS

Dr. Kemp requested an update on the BSCC scope discussions. Ms. Cordle said that a special working group of the Biotechnology Subgroup of the Competitiveness Council had been formed and was producing a new draft. If the Subgroup approved the draft it would go to the Competitiveness Council for approval. It would then be published in the Federal Register for public comment.

FOLLOW-UP ABRAC ACTIONS ON THE GUIDELINES

Dr. Andow proposed that the ABRAC continue to be involved in the redrafting the Guidelines while the EIS is being prepared. He suggested the formation of four working groups to continue to examine the guidelines and propose modifications.

The first working group, as proposed by Dr. Andow, would develop alternative principles such as the development of an algorithm, the definition of safety levels, the basis for familiarity, etc. The second group would develop confinement levels. The third working group would deal with risk/benefit analysis and the definition of acceptable risk. This group might also look at the issue of social impact. The fourth working group would deal with information handling including relations with IBC's, the management of derived information, and the treatment of confidential business information. Four other topics could be addressed in an ad hoc manner. These topics are: examples, context of evaluation, environment, and evaluation of negative results.

Dr. Kemp said that a previous ABRAC is already on record as supporting earlier drafts of the guidelines. He said that as the EIS process moves along, revisions may be made, but it was important to go to the Federal Register with the guidelines as soon as possible. Dr. Kline agreed, stating that ABRAC needed to be involved in the process of modifying the guidelines without stopping their progress. Dr. Osburn said that committee members will be involved in scoping sessions.

Dr. Andow said the four committees would determine alternatives to the Guidelines which would be useful in the EIS process. Dr.

Tolin said she would like to continue to work on issues independent of scoping. She said she would prefer formalized ABRAC involvement. Mr. Robinson said that continued interactions with the public and ABRAC would be in keeping with the spirit of NEPA.

Dr. Korwek asked how the working groups would function in terms of procedures? Dr. Osburn said the initial interactions could take place through the mail or by telephone.

Dr. Andow asked for a sense of the committee on his proposal. He said that if the committee supported it, then the chair could decide how best to implement his proposal. Dr. Osburn said that in his view, the majority of the Commitee favored continued involvement. He said he would work with OAB to determine who would be involved with which group, and what issues each group will cover.

Dr. Young raised the issue of how the Department will treat proposals for field tests in the period until the guidelines are finalized. He said he had asked OAB staff to assist him in drawing up a policy statement which would set in place interim procedures. He said he would like to submit the statement to ABRAC for its review.

Dr. Kemp said that another issue which needs to be addressed is how ABRAC will handle proposals which are submitted for its review. Dr. Young agreed that a clear process needs to be established and he suggested that the committee could review the procedures which OAB had drafted two years ago.

Dr. Young said the September meeting of ABRAC had to be canceled because of lack of resources.

It was moved and seconded to adjourn. The motion passed unanimously.

Dr. Osburn adjourned the meeting at 12:22 p.m.

M P Steinbock

Martha Steinbock
Rapporteur

Alvin L. Young

Alvin L. Young
Executive Secretary

Daniel Jones

Daniel Jones
Rapporteur

Bennie I. Osburn

Bennie I. Osburn
Chair

TABLE OF APPENDICES

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ABRAC Guidelines

Notes from Open Discussion led by D.R. MacKenzie June 21,1990

ABRAC Meeting

Strengths of The Guidelines:

Systematic Design

Integrated Approach to all Organism Classes

Regular and Non Regular Organisms Treated Equally

Orderly Safety Evaluation

Considers Process; Focus is on Product

Based on Molecular Biology

Based on Risk Assessment Principles

Identifies Relevant Risk Attributes

Provide Basis for Relative Familiarity and Genetic Techniques

Biosafety Concern Apparent

Dynamic Process That Builds on Experience

Provides a Focus on Level of Review and Approval

Broad-based Input in its Development

Decentralized Decisions-IBC's Involved

IBC Participation-NIH Linkage

Public Participation

Good Approach to Domesticated Organisms

Conservative Process With Many Check Points

Scope Flexibility(can cover thing not now covered; RNA viruses)

Risk of New Techniques(in Context of Conventional Techniques)

Concerns Based on Parental Organism (too much or not enough?)

Confinement Level Related to Safety Concerns

Focuses on Assessable Environment

Options to The Guidelines:

Set of Principles Rather Than Guidelines

Use Statuatory Solution(s)

Get One Set of Regulations

Linkages of Guidelines to:

The ABRAC Itself

Coordinate Framework (Federal Obligation)

Other Oversight People

NBIAP

Harmonization with Other International Guidelines/ Use Outside USA

Federal/State Roles

Potential Problems with The Guidelines:

Voluntary in Nature and Effect

No Algorithmic Structure

No Straight Forward Discussion of Environment

Does Not Look At Organism by Environment Interactions

Expects Extrapolation From Small Scale Lab to Field Studies

Inconsistent With Ecological Principles

Length of Time For Review

Complex and Confusing

Lack of Clear Discussion of Molecular Processes

Needs "Good Agricultural Research Practice" Definition

Requires Judgment of Significance of the Genetic Modification

Requires Quantification of Risk

Is Subjective in Assigning Numbers

No Clear Risk/Benefit Analysis

Risk May Not Always Be Determined; Certain Available Information May Be Lacking

Too Little Emphasis on Confinement and Anticipated Consequences

Requires Information to"Show No Effect"

Does Uncertainty Equate to Known Risk?(Guidelines Make this Equation)

No Comparisons With EAS and NAS Report

Guidelines Ignore Indigenous Organisms

Does Not Deal With Some Organisms (eg. Nematodes)

No Mechanism to Manage Derived Information For Future Use

Guidelines Lack Specific Examples

Difficulty in Assigning Safety Levels

Applicability May Not Cover All It Needs To Cover

Some GMO'S With Possible Adverse Effects Have Been Excluded

Where is the Data to Support Exclusions?

Exclusions Are Difficult To Understand

Type 1 and Type 2 Cases Need Examples for Credibility

Confinement Needs to be Clarified

There is a Lack of Delineation of All Safety Levels

Confinement Levels Not Applicable to All Organisms

Problems With Composition of IBC's

IBC's Decisions Need To Be Monitored

IBC's and Conflict of Interest, Reviewers and Public Credibility

IBC's and Input into Regulatory Decisions-How to do it ?

CBI Protection Mechanism Needed

Effects & Impacts of Guidelines on:

r-DNA Techniques

Product Development

Biodiversity

DOD Research

Regulations

Food Safety and Food Supply

Scientific and Technical Effects on Environment

Different Value Systems

Morality(Ethics?) and Environment Release

Social Institutions and Structures

Economic Aspects (vs. Conventional breeding)

Public Education

Background Information on Rhizobia Field Experiments
College of Agricultural and Life Sciences
University of Wisconsin-Madison

Eric Triplett, an agronomist at the University of Wisconsin-Madison, plans to test genetically engineered bacteria at two field sites in Wisconsin during the 1990 growing season.

The proposed study will not have an immediate impact on agriculture. However, it could lead to improved yields of several agricultural crops and lessen farmers' reliance on commercial nitrogen fertilizers, many of which are manufactured from natural gas.

The test would be the first time scientists at the UW-Madison has tested a genetically engineered organism in the field. Agracetus tested genetically engineered tobacco plants in Dane County in 1986 and Biotechnica tested genetically engineered bacteria -- similar to those Triplett plans to study -- in Pepin County in 1988 and Dane County in 1989.

Background

Farmers have known for centuries that growing legumes improves the production of the crop that follows them. In 1886 scientists first demonstrated why; bacteria that form nodules on the legumes' roots make nitrogen from the air available to the plants. Some of the nitrogen remains in the soil for the next year's crop.

The amount of nitrogen available in soil often limits plant growth and yields. Most plants deplete soil nitrogen levels. But legumes with nitrogen-fixing bacteria have access to the millions of pounds of atmospheric nitrogen above each acre of soil. Thus they can maintain or even increase the nitrogen level in soils, especially if farmers plow them under as green manure before planting the next crop.

Leguminous plants include important crops such as alfalfa, clover, peas, vetches, beans and soybeans. Legumes and these special bacteria, called rhizobia, can live independently. Although legumes can grow without rhizobia, legume yields are much larger in fields where rhizobia are abundant. Each legume crop has a particular rhizobial variety that nodulates its roots. To insure that the plants in new legume fields form nodules, farmers buy bacterial cultures and introduce them when they plant their crop.

For more than 30 years, the UW-Madison's Department of Bacteriology supplied rhizobial cultures at cost to state farmers. Bacteriologist E.B. Fred, a former president of the UW-Madison, popularized a technique that involved mixing the bacteria with the seed before planting, thus coating each seed with bacteria. Today farmers can purchase rhizobia from one of the many commercial dealers that supply them.

Legumes, especially alfalfa and clover, have played a major role in the development of Wisconsin's highly successful dairy industry. These protein-rich crops provide much of the hay for the state's dairy herds. The ability of the state's dairy farmers to produce these high-quality forages on their farms has been a major factor in their ability to be competitive in the national market for dairy products.

Rational for this line of research

Several scientific groups are developing rhizobial strains with enhanced abilities to fix atmospheric nitrogen in the hopes that these strains will provide crops with more nitrogen and thus improve yields. Triplett believes that such attempts will fail unless scientists address the problems these improved strains face in the soil environment.

Each ounce of soil contains billions of natural soil bacteria, including many thousands to millions of rhizobia. Rhizobia are especially abundant in fields where legumes are growing. Triplett says the native rhizobia in soils cause the problem. Although they don't fix nitrogen as well as the improved strains, the native strains are more competitive than the improved strains at forming nodules.

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Does the project have regulatory approval?

Triplett has notified the U.S. Environmental Protection Agency, the U.S. Department of Agriculture, the National Institutes of Health, the Wisconsin Department of Natural Resources the Wisconsin Department of Agriculture, Trade and Consumer Protection, the UW-Madison Biological Safety Committee and UW-Madison Agricultural Experiment Station of the proposed field trials.

The EPA indicated that they would not request voluntary reporting under the Toxic Substances Control Act. After review, the USDA concluded that the strains modified by Triplett are not plant pests and thus are not regulated articles and do not require a permit from its Animal and Plant Health Inspection Service. The National Institutes of Health asked Triplett to check the scientific literature for information on the T24 bacteriocin.

The Wisconsin DNR indicated that it had no concerns with the proposed test. The Wisconsin DATCP replied that it did not need to issue a permit for the field test. The UW-Madison's Biological Safety Committee and the Agriculture Experiment Station also have approved the study.

Preliminary results

In addition to transferring the genes for bacteriocin production and resistance to a nitrogen-fixing pea rhizobium, Triplett has completed several other related laboratory and field experiments.

He has tested the T24 strain -- the clover strain from Florida that naturally produces the bacteriocin and resists its effects, but does not fix nitrogen -- on clover at the Arlington Research Station. In the first year of the test, the T24 strain formed 70 percent of the nodules when compared with native clover rhizobia in the soil.

Triplett also blocked the genes for bacteriocin production from the T24 strain and showed that without bacteriocin production, the stain was not an effective competitor for nodulation sites on clover in the laboratory.

After moving the genes for bacteriocin production and resistance to the pea rhizobium, Triplett showed that the inserted genes did not lessen the pea rhizobium's ability to fix nitrogen.

Triplett and two coworkers have nearly completed their research on the exact chemical structure of the bacteriocin and plan to study why some rhizobia are sensitive to it. Triplett has developed a bioassay for the bacteriocin that will permit him to measure it in soil samples.

Triplett has also moved the bacteriocin genes into the rhizobia that nodulate clover and snap beans. In laboratory tests on sterile soil, the bacteriocin gave a clover rhizobium with the genes a dramatic advantage in forming nodules when inoculated in experiments with the same bacterium without the bacteriocin genes and one other native rhizobium strain.

Triplett is continuing laboratory tests of pea and clover rhizobia to learn more about how the bacteriocin genes affect competition for nodule formation.

Why do field tests?

Triplett is uncertain if genetically engineered rhizobia will produce the bacteriocin in the soil and how effective it will be in altering the competition for nodulation with native rhizobia. If Triplett or someone else wants to use this strain to improve nitrogen fixation in legumes, it won't receive serious consideration unless it has been shown to work in field trials. A field test will also provide much helpful information about the basic biology of rhizobia and how genes that might alter competitive abilities affect microbial ecology.

Where will the work be done?

The proposed field sites are at the UW-Madison's Arlington and Hancock Agricultural Research Stations located approximately 20 and 80 miles north of Madison, respectively.

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The bacterium Triplett wants to test in the field is Rhizobium leguminosarum bv. viceae, which forms nodules on the roots of field peas. The strain is a better-than-average nitrogen fixer which he received from Lipha Chemical Company (formerly Nitrogen Company) of Milwaukee. That company has a large collection of rhizobia and sells them to farmers for inoculating legume fields. To give the strain a competitive edge over native strains, Triplett moved genes for a bacteriocin into it. Bacteriocins, which are naturally produced by many bacteria, are antibiotic-like compounds that inhibit the growth of a narrow spectrum of other bacteria. The bacteriocin in this study inhibits the growth of native, less-productive rhizobia that form nodules on pea roots.

Triplett may conduct parallel experiments in the field with Rhizobium leguminosarum bv. trifolii, which forms nodules on the roots of clover. On March 13, 1990, he wrote federal and state authorities to ask that the research be expanded to include both peas and clover.

What are the project's goals?

The long-term goal of the research is to develop strains of rhizobia that increase legume productivity by limiting the less effective, native nitrogen-fixing bacteria. The proposed experiments will determine if the bacteriocin-producing strains are competitive in forming nodules in the field, and if they affect other rhizobial populations, the soil biota or the soil environment. The study has broad significance for soil microbial ecology because the ecological importance of bacteriocins is not fully understood.

If the experiments work with peas and clover, there is a good chance the same approach would work on vetch, snap beans and other varieties of the common bean. Triplett has tested the bacteriocin on rhizobia from North America, South America, Europe, Asia, Africa, and Australia that nodulate these plants and found that it inhibited more than 95 percent of those rhizobia.

What is the bacteriocin and where did it come from?

Bacteriocins are highly specific compounds. This one consists of a peptide of 10 amino acids with a thiazoline ring. It inhibits the growth of sensitive strains of the rhizobia varieties that form nodules on snap beans and other common beans, clover and peas. Triplett has tested the bacteriocin against many other bacteria and found that it does not affect them. It does not even inhibit all rhizobia. For example, it does not affect the rhizobia varieties that nodulate alfalfa or cultivated soybeans.

Triplett isolated the genes for the production and resistance of this particular bacteriocin from a specific strain that forms nodules on clover. This strain -- strain 2124 from the USDA's rhizobia collection -- was collected from Florida in 1937. The strain (now often called T24) inhibits nodulation of clover roots by strains of clover rhizobia sensitive to the T24 bacteriocin, but the original clover strain is not useful for agriculture because it does not fix nitrogen.

Scientists know of many other bacteriocins, some of which affect bacterial competition in nature. This is the first instance in which genes have been identified in one rhizobial variety and moved into another variety to give it a competitive advantage in forming nodules.

Who is supporting the research?

In developing this research, Triplett has received funding from the U.S. Department of Agriculture, the Wisconsin Alumni Research Foundation, the College of Agricultural and Life Sciences, and the UW-Madison Graduate School. He has requested funds from UW System Applied Research Program. This project is totally supported by public money.

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How will the field test be done?

Triplett will test the genetically engineered strain's effectiveness in 1- by 5-meter plots planted with 10 rows of either peas or clover. One-third of the seeds in the plots will be coated with the genetically engineered rhizobia that produce the bacteriocin and is resistant to its effects. Another one-third of the seeds will be coated with a nearly identical bacterium; although this genetically engineered strain will resist the bacteriocin's effects, it will not produce the compound. Seeds in the final one-third of the plots will not be inoculated with any rhizobia. To complete all aspects of the field trial, Triplett needs approximately 40 plots at each site.

Will the recombinant bacteria be contained?

Field studies of introduced rhizobia show that these bacteria move very slowly in the soil if at all, apparently because other organisms in the soil keep them from spreading. Triplett does not expect the genetically engineered rhizobia to move more than two inches through the soil during the next three years. He will maintain a 1-meter border around the plots and monitor the soil there for evidence of any movement out of the plots. Triplett is developing methods to detect as few as one cell of the two genetically engineered rhizobia in a gram of soil.

To avoid spread by erosion, Triplett has chosen field sites on flat terrain and that are more than 500 yards from a lake, stream or pond. There is no evidence that rhizobia spread through the air, but he will plant alfalfa around the plots to minimize wind erosion. He will also take meter-deep cores during experiment to check for vertical movement.

If the recombinant rhizobia spread farther into the border than Triplett expects, he will apply sulphur and lower the pH of the soil to 3, which kills rhizobia. If he can still detect any bacteriocin-producing rhizobia after this treatment, he is prepared to have the plots fumigated or to apply an antibiotic to kill any remaining bacteria.

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Chronological Events
Field Release Proposal by Eric Triplett, Agronomy

April 26, 1990

June 7, 1989	Office of Biological Safety forms (SC89-392 and R89-34) submitted by E. Triplett, Agronomy, including details of proposal.
June 14	Institutional Biosafety Committee (IBC) regular meeting: • IBC notified of forthcoming field trial proposal (spring, 1990). • Copies of proposal given to Drs. Spritz and Ludden at meeting.
June 14	Copies of proposal mailed to Drs. Helgeson, Sequeira, and Givnish.
August 9	Copies sent to all IBC members.
Opinion letters received from federal and state agencies.	July 11 — DNR (Reply on file.) September 20 — USDA (Reply on file.) October 10, 1989 & January 29, 1990 — EPA (Reply on file.) October 19 — DATCP (Reply on file.) November 3 — NIH (Reply on file. Review literature for vertebrate toxicity.)
October 19	Proposal sent to IBC agrobiology subcommittee for review. P. Ahlquist, Molecular Virology (N/A) O. Nelson, Genetics E. Bingham, Agronomy T. Tibbetts, Horticulture A. Ellingboe, Plant Pathology R. Burris, Biochemistry J. Handelsman, Plant Pathology (No written response.)
October 20	Proposal sent to ORDA, NIH for review.
October 25	CALS meeting to inform faculty of first UW release.
November 1	Full review by IBC, open meeting. Project approved with conditions: • IBC to be informed of experiment results. • All crops to be destroyed.

College of Agricultural & Life Sciences
News and Features

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College of Agricultural and Life Sciences
University of Wisconsin-Madison

For Immediate Release
For More Information:
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UW SCIENTIST PLANS FIELD STUDIES OF GENETICALLY ENGINEERED MICROBES

Eric Triplett, an agronomist at the University of Wisconsin-Madison, plans to test genetically engineered bacteria in small plots at the Arlington and Hancock Agricultural Research Stations during the 1990 growing season.

The study would be the first time scientists at the UW-Madison have tested a genetically engineered organism in the field. Agracetus tested genetically engineered tobacco plants in Dane County in 1986 and Biotechnica tested genetically engineered bacteria -- similar to those Triplett plans to study -- in Pepin County in 1988 and Dane County in 1989.

The proposed study, which is entirely supported by public funding, could help scientists improve yields of several agricultural crops and help farmers become more sustainable by reducing the amount of commercial nitrogen fertilizer they buy.

However, Triplett says the research is unlikely to have an immediate impact on agriculture.

"The long-term goal of the research is to develop strains of bacteria that will increase the yields and nitrogen-fixing abilities of crops such as peas, beans, soybeans, clover and alfalfa by 10 to 15 percent," Triplett says. "Improved yields would give farmers more product to sell and enhanced nitrogen-fixing abilities would reduce farmers reliance on commercial fertilizers, which are made from increasingly expensive natural gas."

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Bacteriocins are highly specific compounds. The one Triplett is working with inhibits the growth of sensitive strains of the rhizobia that form nodules on snap beans and other common beans, clover and peas. Triplett has tested the bacteriocin against many other bacteria and found that it does not affect them. It does not even inhibit all rhizobia. For example, it does not affect the rhizobia varieties that nodulate alfalfa or cultivated soybeans.

Scientists know of many other bacteriocins, some of which affect bacterial competition in nature. This is the first time genes have been identified in one rhizobial variety and moved into another variety to give it a competitive advantage in forming nodules.

The proposed experiments will determine if the bacteriocin-producing strain is competitive in forming nodules in the field, and monitor its effects on other rhizobia, the soil biota and the soil environment.

Triplett isolated the genes for this particular bacteriocin from a specific rhizobial strain that forms nodules on clover. This strain was collected from Florida in 1937. The strain (now often called T24) inhibits nodulation of clover roots by strains of clover rhizobia sensitive to the T24 bacteriocin; the original clover strain is not useful for agriculture because it does not fix nitrogen.

Triplett has informed the U.S. Environmental Protection Agency, the U.S. Department of Agriculture, the National Institutes of Health, the Wisconsin Department of Natural Resources, the Wisconsin Department of Agriculture, Trade and Consumer Protection, the UW-Madison Biological Safety Committee and UW-Madison Agricultural Experiment Station of the proposed field trials. These agencies and offices have reviewed Triplett's proposed research and have given him permission to proceed with the tests on peas.

In March, Triplett wrote these same agencies asking permission to duplicate the experiment with a genetically altered form of the bacterium that forms nodules on clover roots -- Rhizobium leguminosarum bv. trifolii. He has not yet been notified of any decision.

The field sites for the tests are at the UW-Madison's Arlington and Hancock Agricultural Research Stations located approximately 20 and 80 miles north of Madison, respectively. Triplett will test the genetically engineered pea rhizobium's effectiveness in approximately 40 plots with a total area less than one-tenth of an acre, at each of the research stations.

In developing this research, Triplett has received funding from the U.S. Department of Agriculture, the Wisconsin Alumni Research Foundation, the College of Agricultural and Life Sciences and the UW-Madison Graduate School.

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GWG/6324W/30-32
3/15/90

Steps UW has taken

The UW has consistently taken steps to assure ecological safety of Eric Triplett's proposed field test. Among them:

The biosafety committee told Triplett to conduct his experiments as if he were under federal regulations, even if he is not, and he is doing so;

Triplett double-checked with federal officials to assure himself that they had fully considered their decision not to undertake formal review;

Triplett did conduct experiments in multi-species toxicity of this bacteriocin to assure himself it would not harm non-target species;

Triplett did conduct a literature search on bacteriocins and consulted with a UW-Madison expert on bacteriocins, Dr. Ronald Hinsdill;

The UW notified state, legislative and local leaders, as well as the public, about its plans, even though none of this was required by regulatory agencies;

Triplett consulted with the manager of BioTechnica Agriculture's Sun Prairie field station about problems of safety and containment that might theoretically be encountered;

Triplett and UW agree it is fair to discuss whether the federal regulatory framework is adequate, even though both feel that Triplett's work would have been approved on full review;

Triplett's federal granting agency, USDA, has said in its grant reviews that it wanted to see data from field tests in the course of sustaining funding;

Triplett's project received $64,000 in monitoring funds from other UW agencies to assure safety.

Triplett sent the documentation on his project to NIH, despite the fact that he was not required to do so.

University of Wisconsin-Madison

Office of Biological Safety
1552 University Avenue
Madison, WI 53705
608/263-2037

Biological Safety Committee

University of Wisconsin-Madison Biological Safety Committee Minutes of Regular Meeting

Date April 4, 1990

Present Paul Ebling, John Helgeson, Stanley Inhorn, Geoffrey Letchworth, James Miller, Jessie Price, Robert Radtke, Ilse Riegel, Max Rosenbaum, Luis Sequeira, Lewis Sheffield, Ralph Stauffacher

Absent Raymond Brown, Donn D'Alessio, Thomas Givnish, Lowell Lakritz, Paul Ludden, Ronald Schultz, Ellis Seavey, Richard Spritz, Jack Wunder

Staff Elizabeth Sullivan, Chris Brennan

Call to Order **Dr. Rosenbaum**, acting as chair, called the meeting to order at 1:31 p.m. in the conference room at the State Laboratory of Hygiene. He announced that the portion of the meeting pertaining to environmental release projects was open to the public.

Minutes **Dr. Riegel moved to approve the minutes of the previous meeting as printed.** The motion was seconded by **Dr. Miller** and adopted by voice vote.

rDNA Registration Forms **R89-34 (amendment), E. Triplett, Agronomy**. Dr. Triplett submitted a request to include an additional strain of recombinant *Rhizobium leguminosarum* (bv. *trifolii*) in his field release experiments, resulting in both peas and clover being inoculated. **Dr. Inhorn moved that the Committee approve the amendment. Dr. Miller** seconded the motion and the Committee adopted it by voice vote.

Dr. Rosenbaum informed the Committee that he received a call from the DNR regarding certain individuals' questions about whether the University and Dr. Triplett had submitted this proposal for NIH RAC review. In response, he cited a section of the NIH Guidelines (revisions of Sections I-A and III-A, Federal Register, Vol. 52, No. 163, August 24, 1987) stating that if another federal agency has approved a proposal, it is not necessary for NIH to do so. Nevertheless, the proposal had been sent, along with other federal agency opinions, to Dr. Wivel (Director, ORDA) for his review. It was Dr. Wivel's opinion that ORDA did not need to be involved, and that NIH would accept APHIS' judgment that the experiments do not pose a significant environmental

University of Wisconsin-Madison

Office of Biological Safety
1552 University Avenue
Madison, WI 53705
608/263-2037

Biological Safety Committee

University of Wisconsin-Madison Biological Safety Committee Minutes of Regular Meeting

Date November 1, 1989

Present Raymond Brown, Donn D'Alessio, Paul Ebling, John Helgeson, Stanley Inhorn, Geoffrey Letchworth, Paul Ludden, James Miller, Jessie Price, Robert Radtke, Ilse Riegel, Max Rosenbaum, Luis Sequeira, Ralph Stauffacher, Jack Wunder

Absent Thomas Givnish, Lowell Lakritz, Ronald Schultz, Ellis Seavey, Lewis Sheffield, Richard Spritz

Staff Elizabeth Sullivan

Call to Order Dr. D'Alessio called the meeting to order at 1:30 p.m. in the conference room at the State Laboratory of Hygiene. He announced that the portion of the meeting pertaining to the environmental release project was open to the public.

Minutes The Committee agreed by general consent to approve the minutes of the September 13, 1989 meeting as printed.

Old Business **Laboratory Entry Policy**
After the September meeting the policy statement was redrafted and copies were mailed to all Committee members for review and comment. **Dr. Letchworth** reiterated his opposition to the idea of a policy statement that takes responsibility away from the investigator, who knows the most about his/her laboratory, and gives it to the department chair, who does not want it. He added that the IBC policy as written counters the University code, which states that faculty or other authorized persons have the authority to determine who may enter laboratories or classrooms. **Dr. Rosenbaum** pointed out that the IBC policy is intended as a recommendation to University Administration, which will make its own decision. **Dr. Ludden** also opposed the IBC dictating to investigators how to run their laboratories.

Dr. Brown commented that investigators may be too close to the problem and do not have the wide perspective that, for example, an oversight committee would have. **Dr. Riegel** asserted that it is appropriate for the Committee to deal with this issue, and that the first sentence of the

statement's second paragraph addressed **Dr. Letchworth's** concerns. **Dr. Inhorn** read the policy as a prohibition against anyone entering a laboratory without a valid reason, based on the investigator's judgment.

Dr. Miller moved that the Committee accept the revised laboratory entry policy. Dr. Riegel seconded the motion. **Dr. Helgeson** said that the revised policy draft addresses most of his objections and that he accepts this version. In accordance with Committee procedure, the motion was adopted by a simple majority (voice vote, two dissensions). The policy will be forwarded to University Administration.

R89-34, E. Triplett, Agronomy, "The effects of bacteriocin production on the autoecology of indigenous strains of *Rhizobium*". **Dr. Ludden** presented a review of the environmental release proposal. He prefaced his remarks by informing the Committee that although Dr. Triplett was one of his postdoctoral students and has collaborated with him on review articles and past projects, he (**Dr. Ludden**) has no interest in the present proposal. He asked if any Committee members objected to his review, considering his association with Dr. Triplett. There were no objections.

The proposal, a continuation of Dr. Triplett's laboratory research, involves genes that code for synthesis of a toxin that is produced by natural *Rhizobia* and kills specific rhizobial strains. Dr. Triplett will add the toxin gene to a good nitrogen-fixing rhizobial strain to give it a competitive edge. He will test the new toxin-producing strains in the field to determine if they are more competitive than indigenous strains. This research could be applied to commercial *Rhizobium* strains to make them more competitive.

Dr. Triplett has sent his proposal to the EPA, the USDA/APHIS, the Wisconsin DNR, and DATCP. EPA FIFRA said that the compound is not a pesticide and referred the proposal to TSCA, its toxic substances branch. TSCA said that it will not regulate the compound since Dr. Triplett has no commercial backing. USDA/APHIS said that *Rhizobium* is no longer considered a pest, therefore it will not consider regulation. The DNR deferred to the EPA. DATCP deferred to USDA. Therefore, while no agency has approved the field trial, none feels responsible for regulating it.

In his review of the research, **Dr. Ludden** referred to the National Research Council's recent report that considers the field testing of genetically modified organisms that interact with plants. The Council committee, chaired by Dr. Burris, Biochemistry, drew up a chart outlining points to consider regarding scale, likelihood of adverse environmental effects, and adequate control.

Dr. Ludden said that Dr. Triplett's field test will be small-scale and that laboratory test results and past introduction by Biotechnica rule out the possibility of adverse environmental effects. Also, it is known that *Rhizobia* do not move extensively in the soil and that the toxin is specific to *Rhizobia*.

The study will be conducted at the Arlington and Hancock Farms at sites that do not have direct access to ground water and that will be surrounded by a border row of alfalfa to prevent wind distribution of *Rhizobia*, which are not usually spread by wind.

Dr. Triplett will keep a countersigned log of all transport and use of material during the study. He will give each student and technician working on the project a practices manual with contingency plan in case of accidental release. It is not necessary for Dr. Triplett to post biohazard signs at the field study sites.

Dr. Ludden said that Dr. Triplett has fulfilled all requirements, and he **moved that the Committee approve the proposal.** He reiterated that the project poses no environmental risks and that organism spread (an unlikely event) could be prevented by changing the soil pH of the border row or treating it with antibiotics. **Dr. Sequeira** seconded the motion.

Dr. Sequeira brought up the possibility that the altered strain could became dominant and compete against future strains that might be more desirable. **Dr. Rosenbaum** said that determining this possibility was one purpose of the study. At the experiment's end Dr. Triplett will dispose of all the crops. The altered strain is specific to clover and will not spread to soybeans, alfalfa or broadbeans.

Dr. Triplett's protocol has been distributed to the IBC agrobiology subcommittee. Thus far, Dr. Bingham of that subcommittee said that he found no problem with the study. Others' comments will be considered as they are received.

The protocol has also been submitted to ORDA. Dr. Wivel, ORDA director, commented that he saw no problem, but had concerns over the term "toxin" in the protocol and asked for LD_{50} data. **Dr. Rosenbaum** said he thought the toxin might have been more accurately termed an antibiotic. **Dr. Ludden** said either "toxin" or "bacteriocin" was correct. The Committee agreed by general consent that choice of terminology was not its concern. It adopted the motion to approve Dr. Triplett's release proposal by unanimous voice vote.

Dr. D'Alessio left the meeting at this time and **Dr. Rosenbaum** assumed the duties of chair.

UNIVERSITY OF WISCONSIN-MADISON

COLLEGE OF AGRICULTURAL
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Telephone: 608/262-3026/262-3040
Telex: 26 54 52

DATE: October 31, 1989

TO: Max J. Rosenbaum

FROM: R. H. Burris

RE: Comments on safety of field experiments proposed by Eric Triplett.

This proposal is well thought out. Triplett has done the necessary preliminary experiments and has formulated adequate plans for controlling the modified organism to be added to soil in the field.

There is about 100 years of experience with adding the rhizobia to soil in large numbers and over extensive areas. No problems have arisen over this long period that have constituted a hazard. When E. B. Fred came to Wisconsin in 1913 or 1914, he made field trials with rhizobia and found that their movement in soil was barely detectable. Such experience has been repeated many times since. The minor modifications introduced by Triplett should pose no hazard greater than that of adding wild type rhizobia to the soil.

I see no problem with authorizing this field experiment as planned by Triplett.

R. H. Burris

RHB:mKf

University of Wisconsin-Madison

Office of Biological Safety
1552 University Avenue
Madison, WI 53705
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Biological Safety Committee

University of Wisconsin-Madison Biological Safety Committee Minutes of Regular Meeting

Date June 14, 1989

Present Raymond Brown, Paul Ebling, Stanley Inhorn, Geoffrey Letchworth, Paul Ludden, James Miller, Jessie Price, Robert Radtke, Ilse Riegel, Max Rosenbaum, Ronald Schultz, Ellis Seavey, Richard Spritz, Ralph Stauffacher, Jack Wunder

Absent Donn D'Alessio, Thomas Givnish, John Helgeson, Lowell Lakritz, Luis Sequeira, Lewis Sheffield

Staff Elizabeth Sullivan, Chris Brennan

Call to Order Dr. Rosenbaum, acting as chair, called the meeting to order at 1:32 p.m. in the conference room at the State Laboratory of Hygiene. He announced that the part of the meeting concerning proprietary items would be closed.

Minutes Dr. Schultz moved to approve the minutes of the April 5 meeting as printed. The motion was seconded by Dr. Price and adopted by voice vote.

Old Business **Biomedical Waste Disposal**
At the April 5 meeting the Committee had voted to inform the Chancellor of its concerns regarding medical waste tracking and on-campus incineration. Committee action was prompted by the EPA Medical Waste Tracking Act of 1988 and by a memo from P. Reinhardt, Safety Department, noting insufficient staff available to operate UW incinerators beyond normal scheduling.

A memo was drafted and distributed to Committee members. Dr. Rosenbaum said that although Wisconsin has opted out of participation in the Medical Waste Tracking Act, the University should be prepared for future mandatory programs. Therefore, a letter to the Chancellor was still appropriate. Dr. Inhorn moved that a final draft be written and sent to the Chancellor via the Graduate School Dean. Dr. Riegel seconded the motion.

The Committee then discussed topics the memo should cover, emphasizing incineration issues. Dr. Inhorn modified the motion, specifying that Rosenbaum revise the memo and include appropriate information pointing

and the equivalent gene from pseudorabies virus in bovine cells and test the cells for resistance to bovine herpesvirus. **Dr. Schultz moved to register the project.** Dr. Spritz seconded the motion and it was adopted by general consent, with Dr. Letchworth abstaining. (BL2, Section III-B-3-a)

Other Business

Proposal by G. deZoeten.
Dr. deZoeten has informed the Committee of his work with various plant surface antigens on different plants. The work is conducted in a normal greenhouse. Since Dr. deZoeten is leaving the University, the proposal was presented to the Committee for information only and does not require a formal review.

Proposal by E. Triplett.
Dr. Triplett sought Committee advice on his proposal involving environmental release of a genetically engineered rhizobium strain containing a toxin for other rhizobia. The experiment will be done on a controlled UW farm plot. The investigator has submitted his proposal to the EPA and the USDA, as well as the appropriate state agencies. He will not initiate the experiment until early spring, 1990, but is disseminating information for advice and comment. He still needs to provide additional information, including a site map plan. Over the summer the Biosafety Office will distribute copies of the proposal to all IBC members for review.

Adjournment

Dr. Rosenbaum proposed that the Committee schedule its next meeting for September 1989 unless emergencies arise. The Committee agreed by general consent. The meeting adjourned at 2:49 p.m.

Chris Brennan

Minutes recorded by Chris Brennan

Information Contacts on Triplett Study:

1. First information planning meeting -- Oct. 25, 1989

2. One page briefing sheet to CALS and campus administrators.

3. Second information planning meeting -- Jan. 8, 1990

4. Information release schedule, press release & background paper (attached).

5. First newspaper report of experiment (Chilton Times) -- March 1, 1990

6. Second newspaper report of experiment (Country Today) March 14, 1990

7. About March 19-20., letter, press release and background paper to:
   a. CALS administrators
   b. CALS department chairs
   c. UW campus administrators
   d. Biotech Center
   e. Bio-Safety Committee
   f. System Administrators
   g. Regents via System Administration
   h. Extension Administrators
   i. All Extension County Offices
   j. All Experiment Station superintendents

8. About March 20, press release to:
   a. Daily newspapers
   b. Radio and television
   c. Farm magazines
   d. Trade press

9. About March 20, letter, press release to:
   a. Wisconsin biotech companies and selected others on Biotechnology Center mailing list.
   b. All environmental organizations with Wisconsin offices.
   c. Wisconsin farm and agribusiness organization leaders.

10. About March 19, letter, press release and background paper to:
    a. DNR, DATCP and HSS
    b. SCS, ASCS,FmHA

11. About March 22, letter, press release and background paper to:
    a. Assembly agriculture committee and natural resource committee members.
    b. Senate agriculture committee and science and technology committee members.
    c. Governor's Office
    d. Wisconsin Congressional Delegation

12. March 27, meeting with Rep. Spencer Black (Triplett and Maurer)

13. March 27, phone call to all Representatives and Senators with constituents near the test sites. Sent press release and background paper to each, and invited personal meetings with all who wanted such meetings. None did.

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